IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IDENIX PHARMACEUTICALS, INC., UNIVERSITA DEGLI STUDI DI CAGLIARI, CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE and L'UNIVERSITE MONTPELLIER II, Plaintiffs, v. GILEAD SCIENCES, INC. and GILEAD PHARMASSET LLC, Defendants.	C.A. No. 13-1987-LPS
IDENIX PHARMACEUTICALS, INC., UNIVERSITA DEGLI STUDI DI CAGLIARI, CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE and L'UNIVERSITE MONTPELLIER II, Plaintiffs, v. GILEAD PHARMASSET LLC, Defendant.	C.A. No. 14-109-LPS
IDENIX PHARMACEUTICALS, INC. and UNIVERSITA DEGLI STUDI DI CAGLIARI, Plaintiffs, v. GILEAD SCIENCES, INC. Defendant.	C.A. No. 14-846-LPS

DECLARATION OF JASON MICKLEFIELD, PH.D. REGARDING CLAIM CONSTRUCTION FOR U.S. PATENT NOS. 6,914,054, 7,608,597 & 7,608,600

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1. I have been retained by Gilead Sciences, Inc. and Gilead Pharmasset LLC (collectively "Gilead") in the patent infringement lawsuits referenced above as a technical expert on the subject of fluorinated nucleosides. A copy of my current and complete curriculum vitae is attached to this Declaration as Exhibit A.

2. I understand that the parties in this case will be asking the Court to construe certain terms contained in the claims of United States Patent Nos. 6,914,054, 7,608,597, and 7,608,600. I will refer to these patents individually by their last three digits and to them collectively as the "patents-in-suit." The '054 and '597 patents are titled "Methods and Compositions for Treating Hepatitis C Virus." The '600 patent is titled "Modified 2′ and 3′-Nucleoside Prodrugs for Treating *Flaviviridae* Infections."

3. I understand the '054 patent claims priority back to Provisional Application No. 60/206,585, filed in 2000. I understand the '597 patent is a continuation of the '054 patent, and claims priority back to the same provisional application filed in 2000. I further understand the '600 patent claims priority back to Provisional Application No. 60/392,350, filed in 2002, and Provisional Application Nos. 60/466,194 and 60/470,949, both filed in 2003. I have been asked by Gilead Sciences to provide an explanation, for the benefit of the Court, of how a person having ordinary skill in the art in 2000 to 2003 would have understood certain aspects of the technical disclosures of the patents that relate to disputed claim terms. I have also been asked to explain how certain terms of art used in the patents-in-suit would be understood by a person having ordinary skill in the art as of 2000 to 2003. This declaration contains those explanations.

4. I am prepared to testify before the Court about the explanations contained in this Declaration, if called upon to do so.

5. I am being compensated for the services I render in this case at an hourly rate of

$800 per hour plus reasonable expenses. My compensation is in no way based on the outcome of this litigation. Other than my retention as an expert witness in this matter, I have no prior affiliation with Gilead Sciences, Inc., Gilead Pharmasset LLC, Idenix Pharmaceuticals, Inc., Universita Degli Studi Di Cagliari, Centre National de la Recherche Scientifique, or L'Universite Montpellier II. I have no vested interest, financial or otherwise, in the outcome of the current patent infringement litigation between these companies.

I. EDUCATION, PROFESSIONAL EXPERIENCE, AND QUALIFICATIONS

6. My education and experience is described more fully in the attached curriculum vitae (Ex. A). I nonetheless highlight certain achievements here.

7. I have over 25 years of research experience in bioorganic chemistry, including the design and synthesis of nucleoside and nucleotide analogues, which is particularly relevant to the issues discussed below.

8. I received a Doctor of Philosophy degree from the University of Cambridge in 1993, where I trained in synthetic organic chemistry. I received a Bachelor of Science degree from the University of Hull in 1989.

9. After receiving my Ph.D., I accepted a position as a NATO Postdoctoral Fellow at the University of Washington in Seattle, Washington, under the direction of Professor Heinz G. Floss in the area of bioorganic chemistry, concentrating on biosynthesis and enzymatic chemistry. From 1995 to 1998, I was a Lecturer in Organic Chemistry at Birkbeck College, University of London. In September of 1998, I was recruited to The University of Manchester where I served as Lecturer in Chemistry. I was promoted to Senior Lecturer (2002) and Reader in Biological Chemistry (2003) before being promoted to a Chair in Chemical Biology in 2008. From 2008 until 2011, I was the Director of Research for the School of Chemistry. I am currently a Professor of Chemical Biology at The University of Manchester School of Chemistry

and The Manchester Institute of Biotechnology in Manchester, United Kingdom.

10. I have received several awards in recognition of my research, including a NATO Fellowship (1993-1995). I was elected a fellow of the Royal Society of Chemistry ("RSC") in 2006. In 2008, I received RSC's *Natural Product Reports* (NPR) Lecture award.

11. I am an active participant in a number of professional societies including the RSC Nucleic Acid Group, the RSC Bioorganic Group, the UK Centre of Excellence in Biocatalysis (CoEBio3), and the Engineering and Physical Science Research Council's Chemistry College. I have also served on numerous national and international review panels for the Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Science Research Council (Chemistry Panel), the Deutsche Forschungsgemeinschaft (DFG) - German Research Foundation (International Review Panel for Chemistry), and the European Cooperation in Science and Technology (COST) action (Chemistry Panel). I am also the Director of the BBSRC funded UK Natural Products Network (NPRONET).

12. I serve on the editorial board of *Chemical Biology and Drug Design*, *Frontiers in Chemistry*, and *Synthetic and Systems Biotechnology*. Previously I served on the editorial boards of *Chemical Communications* (2003-2006), *Current Organic Synthesis* (2004-2009), and *Marine Drugs* (2008-2014).

13. I have authored or co-authored more than 80 scientific publications. Of these publications, more than 20 pertain to nucleosides or nucleotides, with approximately 16 relating to nucleoside or nucleotide analogues and one pertaining to the synthesis of 2'-fluorinated nucleoside and nucleotide analogues. Four of my papers also describe using nucleotides and an RNA polymerase enzyme to produce RNA.

14. As part of my work on this matter and in connection with this Declaration, I have

reviewed portions of the materials listed in Exhibit B. Based on my education and experience, and my review of the materials listed in Exhibit B, I have formed certain opinions and made certain observations regarding how a person of skill in the art would have understood certain terms of art in the claims of the patents-in-suit, explained in greater detail in the sections to follow. I believe that my opinions and observations may assist the Court in its determination of the claim construction issues raised by the parties.

II. LEGAL PRINCIPLES

15. In expressing opinions on what I understand might be considered to be legal issues, I have applied the following legal standards conveyed to me by Gilead Sciences's counsel.

16. I understand from Gilead Sciences's counsel that terms in patent claims must be read as they would have been understood by a person of ordinary skill in the art at the relevant time period. I have been advised by Gilead Sciences's counsel that the relevant time period is 2000 to 2003 for the reasons described in paragraph 3.

17. I understand that a hypothetical person of ordinary skill in the art has previously been defined in other proceedings related to this case. I have reviewed and understand those definitions and I agree with them.

18. Specifically, a hypothetical person of ordinary skill in the art related to the '054 patent, the '597 patent, and the '600 patent would include someone with a doctoral degree (Ph.D.) in organic, synthetic or medicinal chemistry, or possibly a related discipline such as pharmacology, and who also had some practical experience (*e.g.,* at least two years) in drug discovery. This person could also be someone with a bachelor's (B.S.) or master's (M.S.) degree in one of these disciplines, but with greater practical experience (*e.g.,* at least four years) in drug discovery. This person would possess certain skills and experience relevant to conducting the

chemical aspects of drug discovery. For example, the artisan would have had experience with standard laboratory techniques used to synthesize organic molecules. The artisan would also have had experience with standard purification and analytical techniques known in the art, such as basic chromatography and nuclear magnetic resonance ("NMR") spectroscopy, respectively. The artisan would have had experience planning and executing syntheses of organic compounds based on methods well known in the art. The artisan would further have had experience performing basic interpretations of biological testing data, for example, interpreting whether biological assay results indicated that a compound had biological activity.

19. Likewise, the hypothetical person of ordinary skill in the art would include someone with a doctoral degree (Ph.D.) in virology, microbiology or molecular biology who also had some practical experience (*e.g.,* at least two years). This person could also have been someone with a bachelor's (B.S.) or master's (M.S.) degree in one of these disciplines but with greater practical experience (*e.g.,* at least four years). This person would possess certain skills and experience relevant to conducting the biological aspects of drug discovery. For example, this person would have had experience testing compounds for biological activity using methods well known in the art. The artisan would have had experience working with cell culture systems, including both conducting and interpreting the results of *in vitro* assays known in the art for screening compounds for biological activity and toxicity.

20. The '054 and '597 patents share a common specification (hereinafter "Common Specification.") For ease of reference, I will generally cite to the specification of the '054 patent to identify elements of the Common Specification, although the reader should understand such citations to encompass the corresponding sections of the '597 patent. Furthermore, my comments and opinions with respect to the '054 specification equally apply to the '597

specification.

III. BASIC CONCEPTS OF NUCLEOSIDE AND NUCLEOTIDE CHEMISTRY UNDERSTOOD BY A PERSON OF SKILL IN THE ART BETWEEN 2000 AND 2003

21. The patents-in-suit relate to modified nucleosides and nucleotides for treating hepatitis C infections.

22. A nucleoside is a chemical compound which is made up of two parts:

(a) a heterocyclic base (which is typically called a base or more precisely, a nucleobase [however both terms can be used interchangeably], as explained further in Section A below); and

(b) a sugar (such as ribose or a deoxyribose [as explained further in Section B below]),

and, as discussed in paragraph 37 below, the sugar and nucleobase are linked by a glycosidic bond.

23. The structures of a ribonucleoside and a deoxyribonucleoside (specifically a 2′-deoxyribonucleoside) are illustrated in Figure 1 below. The deoxyribonucleoside differs from the ribonucleoside at the position known by chemists as the 2′ down position. The ribonucleoside has an oxygen and hydrogen at that position, known as a hydroxyl group (OH). The deoxyribonucleoside has only hydrogen (which convention does not depict) at that position – hence, the name "deoxy."

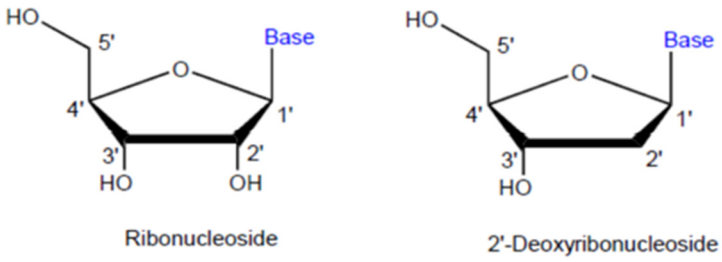


Figure 1. Chemical structures of nucleosides containing ribose (left) and deoxyribose (right).

24. For purposes of the technology at issue in this case, a nucleotide is made up of:

(a) a nucleoside; and

(b) a single or multiple phosphate groups attached at the 5′ position.

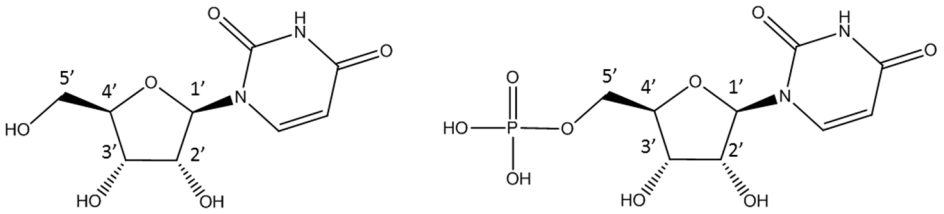


Figure 2. Illustration of a nucleoside and a nucleotide.

25. A **modified nucleoside** or **modified nucleotide** is a nucleoside or nucleotide, respectively, to which at least a single synthetic chemical change has been made relative to its naturally occurring counterpart. I consider the term modified nucleoside or modified nucleotide to be synonymous with the terms **nucleoside analogue** or **nucleotide analogue**, respectively.

26. Nucleotides are the building blocks of **DNA** (**deoxyribonucleic acid**) and **RNA** (**ribonucleic acid**). Specifically, certain 2′-deoxyribonucleotides are the building blocks of DNA and certain ribonucleotides are the building blocks of RNA. See Figure 1 above.

A. Nucleobases

27. A **nucleobase** is a core component of a nucleoside and a nucleotide. Nucleobases naturally occurring in deoxyribonucleosides and deoxyribonucleotides are **adenine (A), guanine (G), thymine (T)** and **cytosine (C)**. Nucleobases naturally occurring in ribonucleosides and ribonucleotides are adenine (A), guanine (G), cytosine (C) and **uracil (U)** (instead of thymine, which is present in deoxyribonucleosides only). For completeness, I note that other naturally occurring nucleobases exist, however these nucleobases are not commonly components of deoxyribonucleotides or ribonucleotides that are incorporated into naturally occurring DNA or

RNA.

28. Positions on the nucleobase are distinguished from those on the sugar in a nucleoside by adopting non-prime numbering for the nucleobase (as illustrated in Figures 3-6 below) and are defined according to agreed upon conventions.

29. The nucleobases listed in paragraph 27 above generally fall into 2 groups:

(a) purine; and

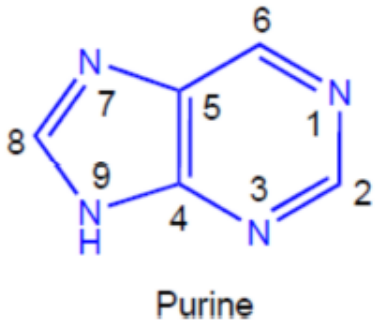
(b) pyrimidine.

30. By definition, a purine is a 5-membered ring fused to a 6-membered ring (each ring containing 2 nitrogen atoms) wherein the nitrogen and carbon atoms are arranged such that:

(a) in the 6-membered ring, the two nitrogen atoms are at the 1 and 3 position;

(b) in the 5-membered ring, the two nitrogen atoms are at the 7 and 9 positions; and

(c) the carbon atoms are at the 2, 4, 5, 6 and 8 positions, as illustrated in Figure 3 below:



Purine

Figure 3. Structure of purine.

31. Guanine and adenine are members of a class collectively called **purines**. The structures of guanine and adenine nucleobases are illustrated in Figure 4 below:

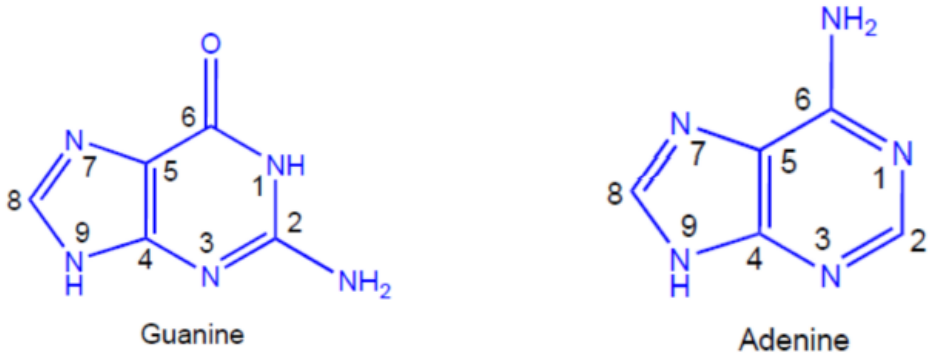


Figure 4. Structures of guanine and adenine nucleobases.

32. By definition, a pyrimidine is a single 6-membered ring (containing 2 nitrogen atoms) wherein the nitrogen atoms are at the 1 and 3 position in a so-called "1, 3-relationship," and the carbon atoms are at the 2, 4, 5 and 6 position, as illustrated in Figure 5 below:

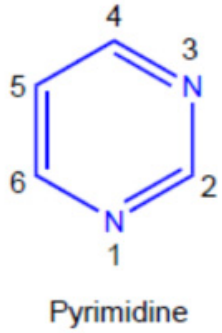


Figure 5. Structure of pyrimidine.

33. Thymine, cytosine, and uracil are members of a class collectively called **pyrimidines**. The structures of cytosine (C), thymine (T) (present in naturally occurring DNA only) and uracil (U) (present in naturally occurring RNA only) nucleobases are illustrated in Figure 6 below:

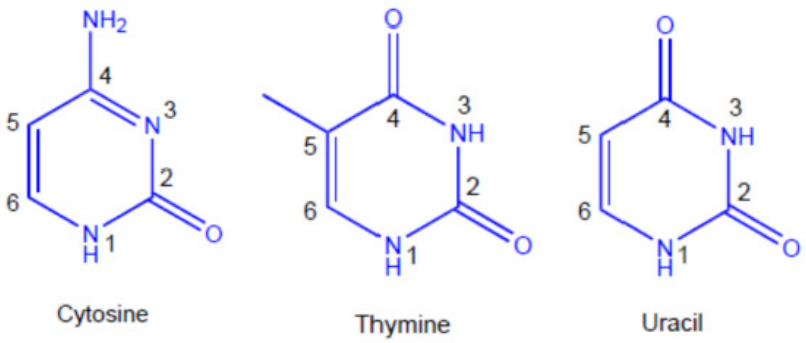


Figure 6. Structures of cytosine, thymine and uracil nucleobases.

34. As noted in paragraph 25 above, modifications can be made to the naturally occurring nucleobases to produce a nucleoside analogue or nucleotide analogue when the modified nucleobase is linked to the sugar (which may itself also be modified, see Section B below).

B. Sugars

35. The **sugar** component of a nucleoside or a nucleotide is a cyclic sugar. The sugar component of a natural ribonucleoside or a natural ribonucleotide is **ribose,** which is a 5 carbon sugar. The structure of ribose is shown below in Figure 7.

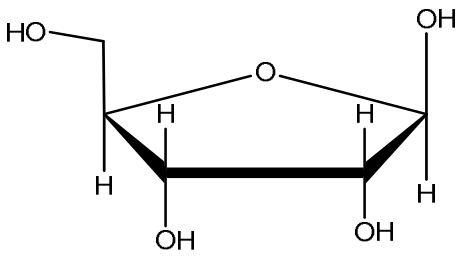


Figure 7. The structure of ribose.

36. The ring of a ribose contains four carbon atoms and one oxygen atom. As noted earlier, the carbon atoms of the sugar in a nucleoside are identified using prime numbering (see paragraph 28), as depicted in the figure below:

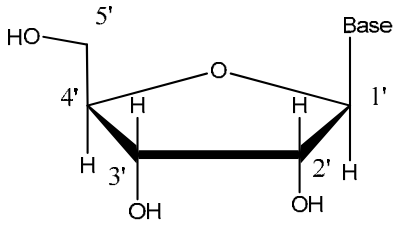


Figure 8. Structure illustrating the numbering convention of the sugar component of nucleosides.

37. As noted in paragraph 22 above and as illustrated in Figure 9 below, the sugar and nucleobase of a nucleoside are connected by a chemical linkage referred to as a glycosidic bond (colored in green). In the naturally occurring nucleosides and nucleotides found most commonly in DNA and RNA, the nucleobase is attached by a nitrogen (N) atom to the anomeric carbon (1′-carbon position) of the sugar ring, as shown in Figures 9, 10, and 11 below.

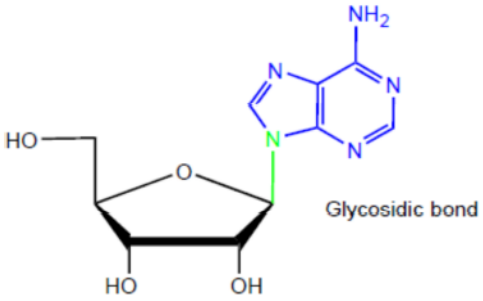


Figure 9. The glycosidic bond of adenosine.

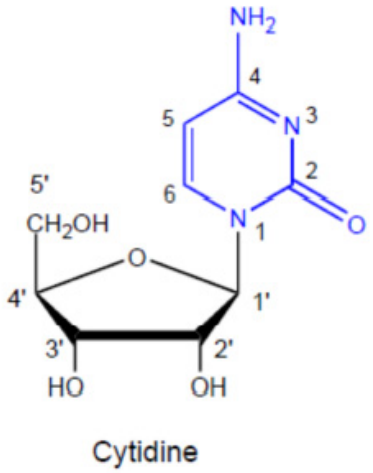


Figure 10. Numbered structure of cytidine.

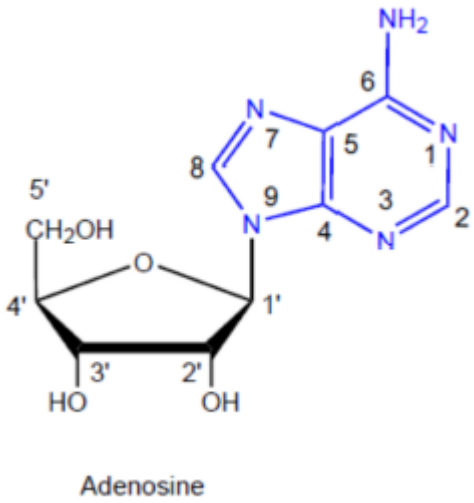


Figure 11. Numbered structure of adenosine.

C. Nomenclature and terminology

38. As discussed in paragraph 27 above, adenine, guanine, thymine, cytosine and uracil are naturally occurring nucleobases. The corresponding nucleosides containing those nucleobases are referred to as **adenosine, guanosine, thymidine, cytidine,** and **uridine**, respectively.

39. In general, the stereochemical, or three-dimensional, configuration of nucleosides is described using **D and L terminology** and **alpha (α) and beta (β) terminology**. This

terminology originates from carbohydrate chemistry and, as such, is not terminology that is limited to nucleosides.

40. The categorization of a sugar as **D** or **L** is determined by reference to the orientation of the substituent at the 4′-position.

41. The **α and β terminology** refers to the orientation of the nucleobase at the 1′-position relative to the orientation of the substituent (or group) at the 4′-position. As illustrated in Figure 12 below, where the nucleobase and substituent at the 4′-position (which is CH_2OH in the example below) are:

(a) on the same side of the ring, a nucleoside is classified as a **β-nucleoside**; and

(b) on opposite sides of the ring, a nucleoside is classified as an **α-nucleoside**.

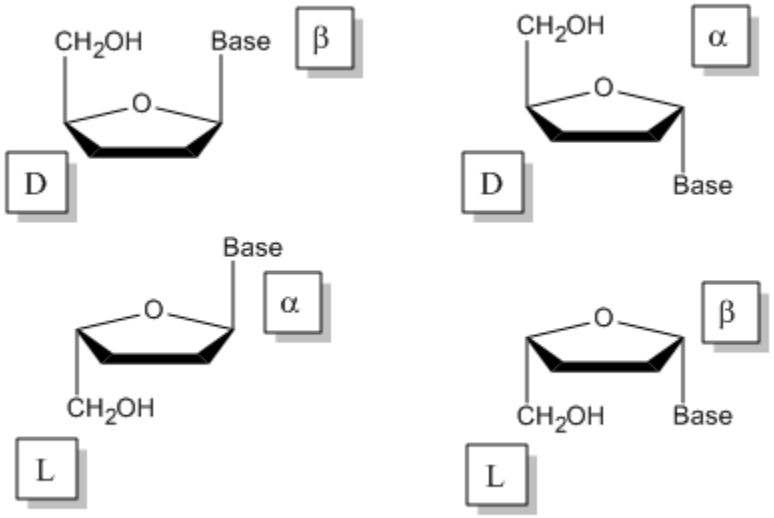


Figure 12. Illustration of D/L and α/β configurations.

42. Although the α and β terminology is based on the orientation of the nucleobase relative to the substituent (group) on the 4′-position, the α and β terminology is sometimes loosely used to describe whether substituents at any position on the sugar are on the α-face or β-

face of the sugar ring.

43. The α and β terminology and the D and L terminology can be used together to describe the orientation and stereochemistry of nucleosides. For example, a nucleoside chemist understands that the name *β-D-2′,6-dimethyl-cytidine* (as illustrated in Figure 13 below) indicates that:

> (a) the compound is derived from the nucleoside cytidine. The β-D indicates that the stereochemistry of the nucleoside is of a particular configuration, in this case in the configuration of the natural nucleoside;
>
> (b) there are two methyl groups in the nucleoside (thus "dimethyl"), one at the 2′-position on the sugar and one at the 6-position of cytidine; and
>
> (c) OH groups are present at the 2′ down, 3′ down, and 5′ positions of the sugar.

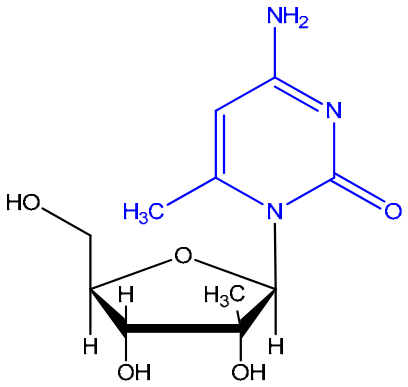


Figure 13. Structure of β-D-2′,6-dimethyl-cytidine.

D. Prodrugs

44. A **prodrug** is a modified form of a parent drug. It is this parent compound that is either (i) the active form or (ii) further metabolized by the body to the active form. A prodrug typically has beneficial properties compared to the parent compound, including (but not limited to) improved chemical stability, improved toxicity profile, and improved pharmacokinetic profile.

IV. THE TERM "NUCLEOSIDE" AS USED IN THE CLAIMS OF THE '054 PATENT

45. It is my opinion that a person of ordinary skill in the art would have understood the term "nucleoside," as used in the context of the patents-in-suit, to mean a compound comprising a base and sugar, with a hydroxyl group at the 5′ position of the sugar.

A. "Nucleoside" has a plain and ordinary meaning

46. As noted above, "nucleoside" has a plain and ordinary meaning to those of skill in the art: a compound comprising a base coupled to a sugar containing a 5′ hydroxyl group. As described above in Section III and as used in the context of the technology at issue, nucleosides differ from nucleotides, which contain a mono-, di-, or tri-phosphate at the 5′ position. Nothing in the context of the patents indicates to me that "nucleoside" (or, for that matter, "nucleotide") as used in the patents is intended to convey a different meaning.

47. The literature is consistent with my understanding of the term "nucleoside." For example, in a book chapter entitled "Oligonucleotides and Nucleic Acids" by Lemke, the author includes the following structures and descriptions of nucleosides and nucleotides. THOMAS L. LEMKE, REVIEW OF ORGANIC FUNCTIONAL GROUPS 107 (David B. Troy et al. eds., 4th ed. 2003) (Ex. C).

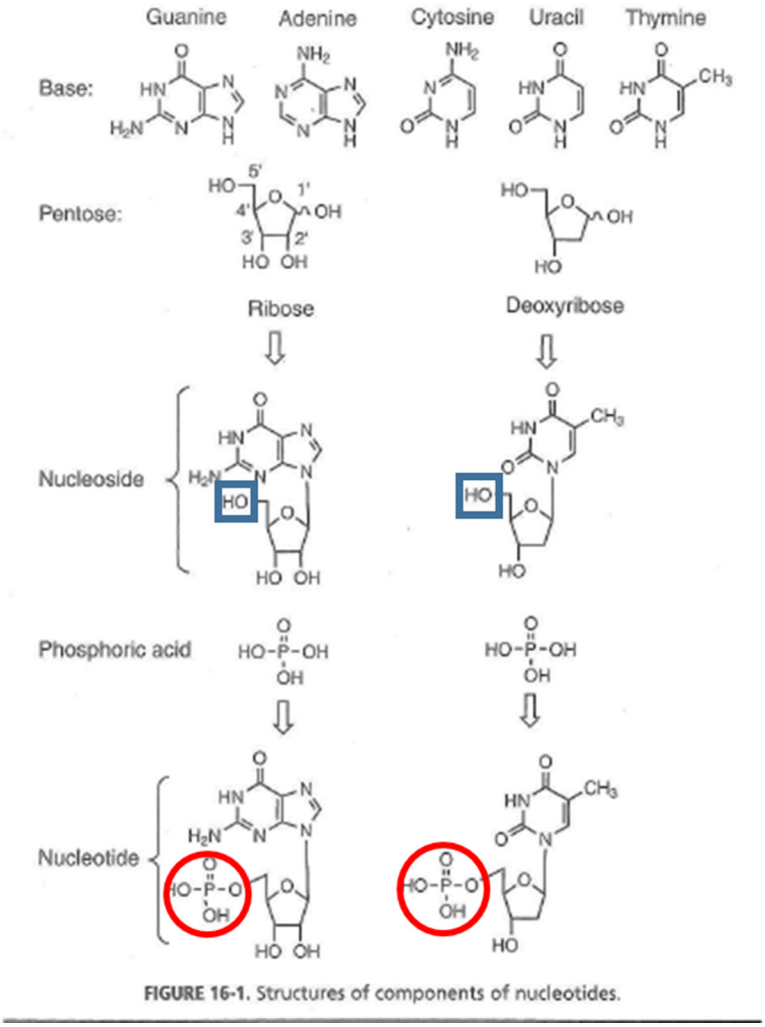


Figure 14. Structures of nucleosides and nucleotides from *Review of Organic Functional Groups*.

48. As illustrated in Figure 14, the author uses "nucleoside" to describe the structure of a base coupled to a sugar containing a hydroxyl group (OH, squared in blue) at the 5′ position. The author uses the term "nucleotide," by contrast, to describe a base coupled to a sugar containing a mono-phosphate (circled in red) at the 5′ position. This is consistent with a skilled artisan's understanding of the term "nucleoside" and "nucleotide."

49. As an additional example, in *Lehninger Principles of Biochemistry*, the term "nucleotide" is used to describe the structure of a base coupled to a sugar containing a mono-

phosphate group at the 5′ position, as shown in Figure 15 below. DAVID L. NELSON & MICHAEL M. COX, LEHNINGER PRINCIPLES OF BIOCHEMISTRY 271-72 (Katherine Ahr et al. eds., 5th ed. 2008) (Ex. D).

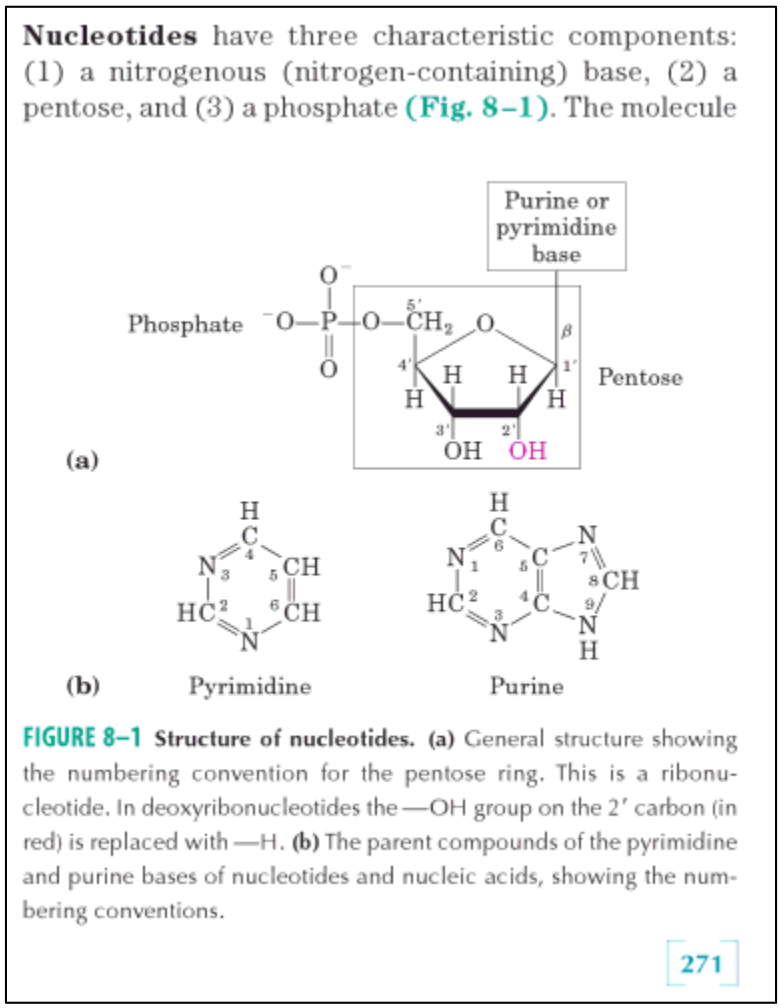


Figure 15. Structure and description of nucleotides from *Lehninger Principles of Biochemistry*.

50. The text states "[n]ucleotides have three characteristic components: (1) a nitrogenous (nitrogen-containing) base, (2) a pentose, and (3) a phosphate. The molecule without the phosphate group is called a nucleoside." *Id.* (internal references omitted). The structure of the nucleotide contains a mono-phosphate group at the 5′ position.

51. As another example, in a textbook entitled "Principles of Biochemistry," the

structures in Figure 16 are presented in a box entitled "Nucleoside and Nucleotides" to describe the difference between nucleosides and nucleotides. H. ROBERT HORTON ET AL., PRINCIPLES OF BIOCHEMISTRY 200 (John Challice et al. eds., 3d ed. 2002) (Ex. E).

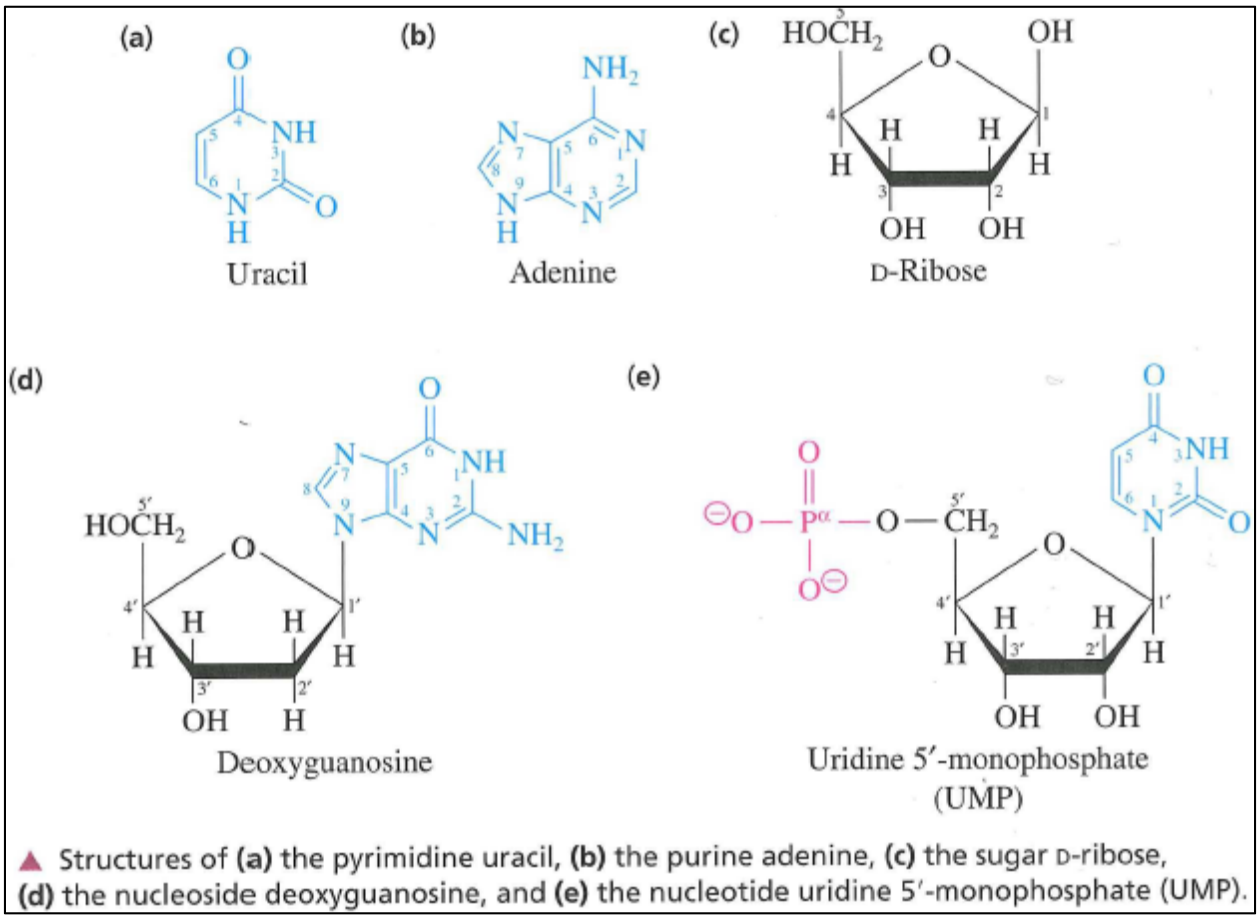


Figure 16. Structures of nucleosides and nucleotides from *Principles of Biochemistry*.

52. The textbook's description of the figure shown in Figure 16 identifies structure (d) as a nucleoside and structure (e) as a nucleotide. Structure (d) contains a hydroxyl group at 5′ whereas structure (e) does not. Instead structure (e), a nucleotide, contains a mono-phosphate group at the 5′ position.

53. Collectively, the literature uses the term "nucleoside" synonymously with a base coupled to a sugar with a hydroxyl group at the 5′ position and uses the term "nucleotide" to describe nucleosides containing a mono-, di-, or tri-phosphate at the 5′ position. In my opinion,

people skilled in the art as of 2000 to 2003 would have had the same understanding of nucleosides and nucleotides.

B. The patent specification aligns with the plain and ordinary meaning of nucleoside

54. The term "nucleoside" is not defined in the patents. However, the term appears in independent claims 1-9, 22-24, and 25 of the '054 patent.

55. Independent claims 1-9 and 22-24 recite "[a] method for treatment of a Hepatitis C virus infection in a human in need thereof, comprising administering to said human an antivirally effective amount of a β-D nucleoside compound of the structure . . ." followed by Haworth projections (drawings) of nucleosides. To illustrate, Figure 17 below contains all the structures depicted in claims 1-9 and 22-24 of the '054 patent. Each of the nucleosides depicted in independent claims 1-9 and 22-24 contain a hydroxyl group at the 5′ position of the sugar.

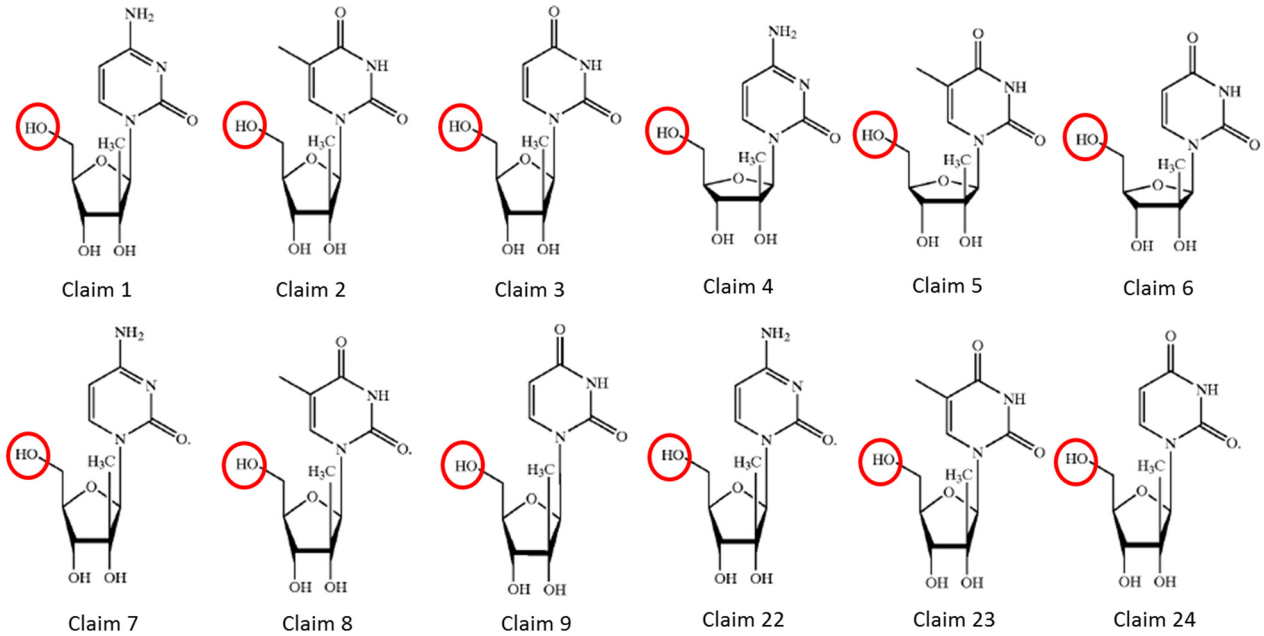


Figure 17. Structures of "nucleosides" depicted in claims 1-9 and 22-24 of the '054 patent.

56. Claim 25 recites "[a] method for treatment of a Hepatitis C virus infection in a host in need thereof, comprising administering to said host an antivirally effective amount of a β-

D-2′-C-branched pyrimidine nucleoside." Unlike claims 1-9 and 22-24, no structure follows independent claim 25.

57. Thus, when looking at the plain meaning of the claims, a person of ordinary skill in the art would have understood the term "nucleoside" to refer to a compound comprising base and sugar moieties, with a hydroxyl group at the 5′ position.

58. I understand Idenix proposes to define "nucleoside" as merely a base coupled to a sugar. In my opinion, that definition is overly broad and would encompass both nucleosides and nucleotides. I also observe that, when Idenix wishes to denote a nucleotide, it does so explicitly by using the phrase "nucleosides or a phosphate thereof." For example, claim 1 of the '597 patent states "[a] method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine β-D-2′-methyl-ribofuranosyl **nucleoside or a phosphate thereof**, or a pharmaceutically acceptable salt or ester thereof." ('597 Patent, claim 1 (emphasis added); *see also* '597 Patent, claims 2-33.) Notably all the claims of the '054 patent simply claim "nucleosides" and do not include the phrase "or a phosphate thereof." Thus, in my opinion, persons of skill in the art would have understood "nucleoside" in the context of the claims of the '054 patent to be consistent with the definition I provide at paragraph 46 above. That is, it is a base coupled to a sugar with a hydroxyl group at the 5′ position.

V. THE TERM "β-D-2′-METHYL-RIBOFURANOSYL NUCLEOSIDE" AS USED IN THE CLAIMS OF THE '597 PATENT

59. The term "β-D-2′-methyl-ribofuranosyl nucleoside" does not appear in the specification of the '597 patent. However, in my opinion, a person of ordinary skill in the art would have understood that the term "β-D-2′-methyl-ribofuranosyl nucleoside," as recited in the claims of the '597 patent, consistent with its plain and ordinary meaning to a person of skill in

the art, refers to a very specific structure—namely, a β-D-nucleoside that includes a five member sugar ring with a methyl group in the 2′ up position and hydroxyl groups at the 2′ down and 3′ down positions.

A. "β-D-2′-methyl-ribofuranosyl nucleoside" has a plain and ordinary meaning

60. In common chemical nomenclature, which is the type of nomenclature used in the claims of the patents-in-suit, the "β-D-2′-methyl-ribofuranosyl nucleoside" term requires a nucleoside comprising a ribofuranose sugar, modified with a methyl group at the 2′ position, coupled to a base in the β-D configuration.

1. Ribofuranose

61. Ribofuranose has a plain and ordinary meaning. Specifically, it is a five membered sugar, ribose, which contains hydroxyl groups at the 2′ down and 3′ down positions. The structure of ribose is depicted in Figure 7 above (and reproduced again below).

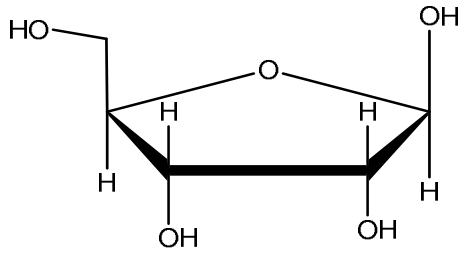


Figure 7. The structure of ribose.

62. The literature is consistent with my understanding of β-D-ribofuranose as used in the context of the claims of the '597 patent. For example, in *Essentials of Organic Chemistry*, the author includes the following structure of β-D-ribofuranose in the context of nucleosides. PAUL M. DEWICK, ESSENTIALS OF ORGANIC CHEMISTRY 228 (2006) (Ex. F).

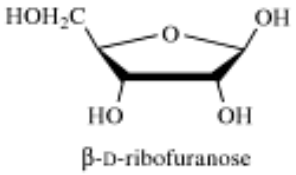


Figure 18. Structure of β-D-ribofuranose from *Essentials of Organic Chemistry*.

63. This illustration demonstrates that β-D-ribofuranose is a five member ring, with hydroxyl groups at the 2′ and 3′ down positions. Skilled artisans would have understood that HO and OH, as depicted in Figure 18, both represent hydroxyl groups.

64. As another example, a chapter entitled "Covalent Features of the Nucleic Acids" in *Informational Biopolymers of Genes and Gene Expression* presents the following structure of a β-D-ribofuranose sugar attached to a base. R.D. BLAKE, INFORMATIONAL BIOPOLYMERS OF GENES AND GENE EXPRESSION 136 (Ann B. McGuire ed., 2005) (Ex. G).

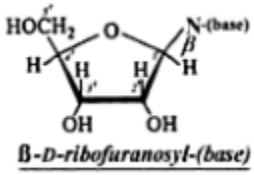


Figure 19. Structure of β-D-ribofuranose sugar attached to a base from *Informational Biopolymers of Genes and Gene Expression*.

65. This drawing depicts the structure of β-D-ribofuranose as a five member ring with hydroxyl groups (OH) at the 2′ and 3′ down positions.

66. Collectively, these references use the term β-D-ribofuranose synonymously with a five member sugar ring containing hydroxyl groups at the 2′ down and 3′ down positions. In my opinion, persons of skill in the art would have had the same understanding of β-D-ribofuranose in the context of the patents-in-suit.

2. 2′-methyl

67. As described above in Section III, under traditional naming conventions, the positions of the carbons in the sugar ring of nucleosides and nucleotides are denoted with a prime notation (by the symbol ′) (as illustrated in Figures 10 and 11 above) to distinguish these carbon atoms from the atoms of the base. Thus, persons of skill in the art would have understood that the term "2′-methyl" indicates that a methyl group is present at the 2′ position of the ribose sugar ring in the nucleoside. Therefore, a "β-D-2′-methyl-ribofuranosyl nucleoside" contains hydroxyl groups at the 2′ (down) and 3′ (down) positions, and a methyl group at the 2′ position. Persons of skill in the art would have understood the methyl group at 2′ to be oriented "up" on account of the presence of a hydroxyl group at 2′ down, as required by the plain and ordinary meaning of the term ribofuranose.

68. Thus, combining the understanding of skilled artisans' definitions for "2′-methyl" and "β-D-ribofuranosyl nucleoside," persons of skill in the art would have understood the phrase "β-D-2′-methyl-ribofuranosyl nucleoside" to describe a β-D-nucleoside that includes a five member sugar ring with a methyl group in the 2′ up position and hydroxyl groups at the 2′ down and 3′ down positions.

B. The prosecution history is consistent with the plain and ordinary meaning of "β-D-2′-methyl-ribofuranosyl nucleoside"

69. My review of the prosecution history of the '597 patent further confirms my opinion that persons of skill in the art would have understood that the term "β-D-2′-methyl-ribofuranosyl nucleoside" means a five member sugar ring with a methyl group in the 2′ up position and hydroxyl groups at the 2′ down and 3′ down positions.

70. For example, in a Response to Office Action dated March 10, 2006, Idenix stated that "[s]upport for the pending claims can be found throughout provisional application 60/206,585. . . . Specifically, the compound with formula VI on page 23 discloses a **β-D-2′-**

methyl ribofuranosyl nucleoside, wherein base is a purine or pyrimidine base, R^4 may be alkyl, and R′ may be H." (March 10, 2006 Remarks at 5 (emphasis added) (Ex. H).) As shown below, Formula VI depicts a base coupled to a sugar containing hydroxyl groups at the 2′ down and 3′ down positions. (Provisional Application No. 60/206,585 at 23 (Ex. I).) In the Provisional Application No. 60/206,585, Idenix defined "alkyl" to specifically include methyl. (*Id.* at 23.) Thus, Idenix itself identified Formula VI, which contains 2′ down and 3′ down hydroxyl groups, as a ribofuranosyl nucleoside. Persons of skill in the art would have had a similar understanding.

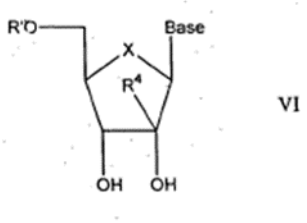


Figure 20. Formula VI from Provisional Application No. 60/206,585, cited in Applicants' Remarks dated March 10, 2006.

71. I understand Idenix proposes to define "β-D-2′-methyl-ribofuranosyl nucleoside" as a "β-D-nucleoside that includes a five member sugar ring with a methyl group in the 2′ up position and non-hydrogen substituents at the 2′ down and 3′ down positions." I believe this definition is overly broad. As explained above, persons of skill in the art would have understood the term "ribofuranosyl nucleoside" to refer to a very specific compound with hydroxyl groups at the 2′ down and 3′ down position. In my opinion, Idenix's construction, which allows for any non-hydrogen substituents at the 2′ and 3′ down positions, is inconsistent with the plain and ordinary meaning of "ribofuranosyl" and Idenix's own statements made during the prosecution of the '597 patent, as described in paragraph 70 above.

VI. THE TERM "β -D-2′-C-BRANCHED PYRIMIDINE NUCLEOSIDE" AS USED IN THE CLAIMS OF THE '054 PATENT

72. I understand the parties agree that the term "β-D-2′-C-branched pyrimidine

nucleoside" requires a β-D pyrimidine nucleoside having two non-hydrogen substituents at the 2' position, at least one of which is connected at the 2′ position through a carbon-to-carbon bond. I further understand the dispute involves whether or not fluorine at the 2′ down position is excluded from the definition.

73. For the reasons set forth below, it is my opinion that a person of ordinary skill in the art would have understood the term "β-D-2′-C-branched pyrimidine nucleoside" as used in the '054 patent, to mean a β-D pyrimidine nucleoside with two non-hydrogen substituents at the 2′ position, at least one of which is connected at the 2′ position through a carbon-to-carbon bond, and no fluorine at the 2′ down position.

A. Definition of the term "Branched"

74. In the context of organic chemistry, when a carbon atom in a compound is connected to one or two other carbon atoms in a linear manner, the connection is referred to as straight-chain or linear. In contrast, when a carbon atom in an organic compound is connected to more than two other carbon atoms, the connections are now considered non-linear and commonly referred to as branched.

75. *Fundamentals of Organic Chemistry* provides the following illustration explaining the term "branched." JOHN MCMURRY, FUNDAMENTALS OF ORGANIC CHEMISTRY 46 (Lisa Lockwood et al. eds., 7th ed. 2011) (Ex. J).

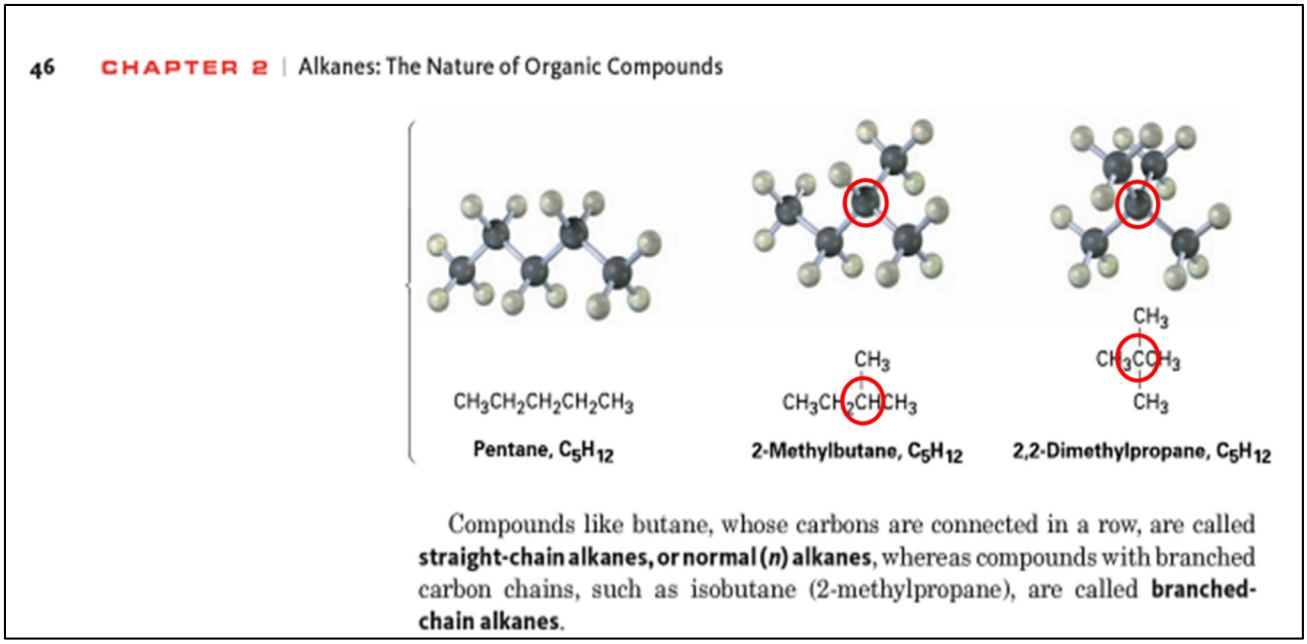


Figure 21. Structures of a straight-chain alkane and branched alkanes from *Fundamentals of Organic Chemistry*.

76. The text identifies pentane as a straight-chain alkane because the carbon atoms are connected in a linear manner. *Id.* In contrast, the text refers to 2-methylbutane as "branched." *Id*. As highlighted by the red circle (added), 2-methylbutane is referred to as "branched" because the circled carbon is connected to other carbon atoms in a non-linear, or branched, fashion. For the same reason, skilled artisans would have referred to 2,2'-dimethylpropane as "branched."

77. That general definition of "branched" as set out in paragraph 75 is too broad in the context of the Idenix patents. In my opinion, skilled artisans reviewing the specification of the '054 patent would conclude that "2′-C-branched pyrimidine nucleoside" excludes fluorine as an option for the substituent at the 2′ down position.[1]

B. The '054 patent defines "2′-C-branched" to exclude fluorine

[1] As discussed in paragraph 20 above, the specifications of the '054 and '597 patents are identical. Thus, my comments pertaining to the '054 patent specification apply equally to the '597 patent specification.

78. The term "2′-C-branched," while identifying one substituent at the 2′ position (a carbon containing group), does not specifically identify the other. The specification of the '054 patent, however, does define the other substituents explicitly in a lengthy list. The specification of the '054 patent uses the phrase "2′-C-branched" at col. 47, lines 5-6 as follows:

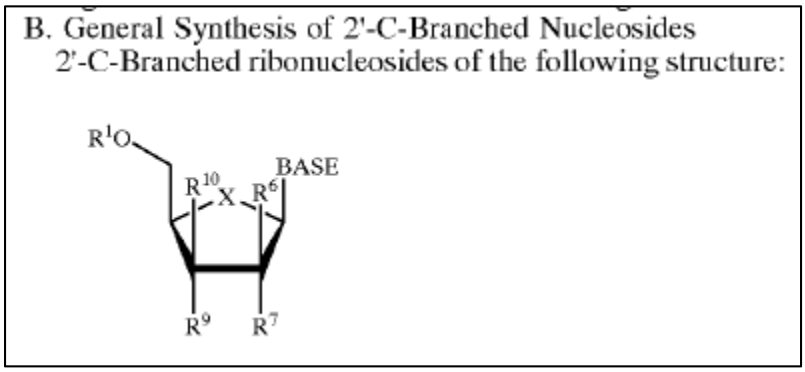


Figure 22. Description of 2′-C-branched nucleosides from the '054 patent specification.

79. In describing the substituents at the 2′ down position, referred to as R^7 in Figure 22 above, the patent recites: "hydrogen,[2] OR^2, hydroxyl, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, —C(O)O(alkyl), —(C(O)O(lower alkyl), —O(acyl), —O(lower acyl), —O(alkyl), —O(lower alkyl),—O(alkenyl), ***chlorine, bromine, iodine***, NO_2, NH_2, —NH(lower alkyl), —NH(acyl), —N(lower alkyl)$_2$, —N(acyl)$_2$." ('054 Patent 47:17-23 (emphasis added).) Despite the fact that this list includes thousands of possible substituents at the 2′ down position, including three other halogens (chlorine, bromine and iodine— compounds that are in the same chemical group as fluorine), fluorine itself is absent. A person of skill in the art would therefore have understood that fluorine is not included as an option for the 2′ down

[2] In the Applicant Remarks dated June 16, 2003, Idenix disclaimed hydrogen at the 2′ position, noting that "[t]he unifying concept in the remaining claims is that each is a pyrimidine nucleoside that has two-non-hydrogen substituents in the 2′-position of the nucleoside, which represents the core of the invention." June 16, 2003 Remarks, at 11 (emphasis in original) (Ex. K).

substituent. Thus, in view of the specific disclosure of the '054 patent, I believe that a person having ordinary skill in the art would have understood "2′-C-branched" to exclude fluorine at the 2′ down position.

80. The remainder of the specification further supports my opinion. Despite not listing fluorine as a possible 2′ down substituent, Idenix included fluoro in the definition of functional groups to be included at the 2′ **up** position. (*See* '054 Patent 47:40-41 ("R^6 is an alkyl, chloro-, bromo-, ***fluoro***-, iodo-alkyl (i.e. CF_3), alkenyl, or alkynyl (i.e., allyl)") (emphasis added).) Furthermore, throughout the rest of the specification, Idenix used the term "fluoro" hundreds of times, but never once to describe fluorine at the 2′ down position in 2′-C-branched nucleosides. Rather, every embodiment disclosed in the specification **excludes** fluorine at the 2′ down position. In my opinion, the fact that the patent discusses fluorine extensively elsewhere, but chooses not to list it as a possible 2′ down substituent in a "2′-C-branched" nucleoside, informs a person skilled in the art that 2′ down fluorine is not intended to be included as part of that structure.

81. Skilled artisans reading the specification of the '054 patent would have recognized that fluorine at the 2′ down position was excluded from the term "2′-C-branched" nucleoside. Thus, skilled artisans would have interpreted the claim term "β-D-2′-C-branched pyrimidine nucleoside" to exclude fluorine from the 2′ down position.

VII. THE TERM "β-D-2′-C-BRANCHED PYRIMIDINE RIBONUCLEOSIDE" AS USED IN THE CLAIMS OF THE '054 PATENT

82. I understand the parties agree that the term "β-D-2'-C-branched pyrimidine ribonucleoside" requires a β-D pyrimidine ribonucleoside having a non-hydrogen substituent at the 2′ up position that is connected at the 2′ position through a carbon-to-carbon bond. I further understand the dispute involves the functional groups required at the 2′ and 3′ down positions.

83. It is my opinion that a person of ordinary skill in the art would have understood the term "β-D-2'-C-branched pyrimidine ribonucleoside" as used in claim 26 of the '054 patent, consistent with its plain and ordinary meaning, to mean a β-D pyrimidine nucleoside with a non-hydrogen substituent at the 2′ up position that is connected at the 2' position through a carbon-to-carbon bond, and hydroxyl groups at the 2′ down and 3′ down positions.

84. In common chemical nomenclature, which is the type of nomenclature used in the claims of the patents-in-suit, the term "β-D pyrimidine ribonucleoside" requires a "ribonucleoside" coupled to a pyrimidine base in β-D configuration.

A. Definition of "ribonucleoside"

85. Persons of ordinary skill would have understood that the term "ribonucleoside" meant a ribose nucleoside. Like ribofuranose, ribose has a plain and ordinary meaning known to skilled artisans. In particular, ribose means a specific five membered sugar which contains hydroxyl groups at the 2′ down and 3′ down positions. See Figure 7 above.

86. Literature examples support this understanding of the phrase "ribonucleoside." *Organic Chemistry* by Smith provides the following definition for ribonucleoside. MICHAEL B. SMITH, ORGANIC CHEMISTRY 1451 (2011) (Ex. L).

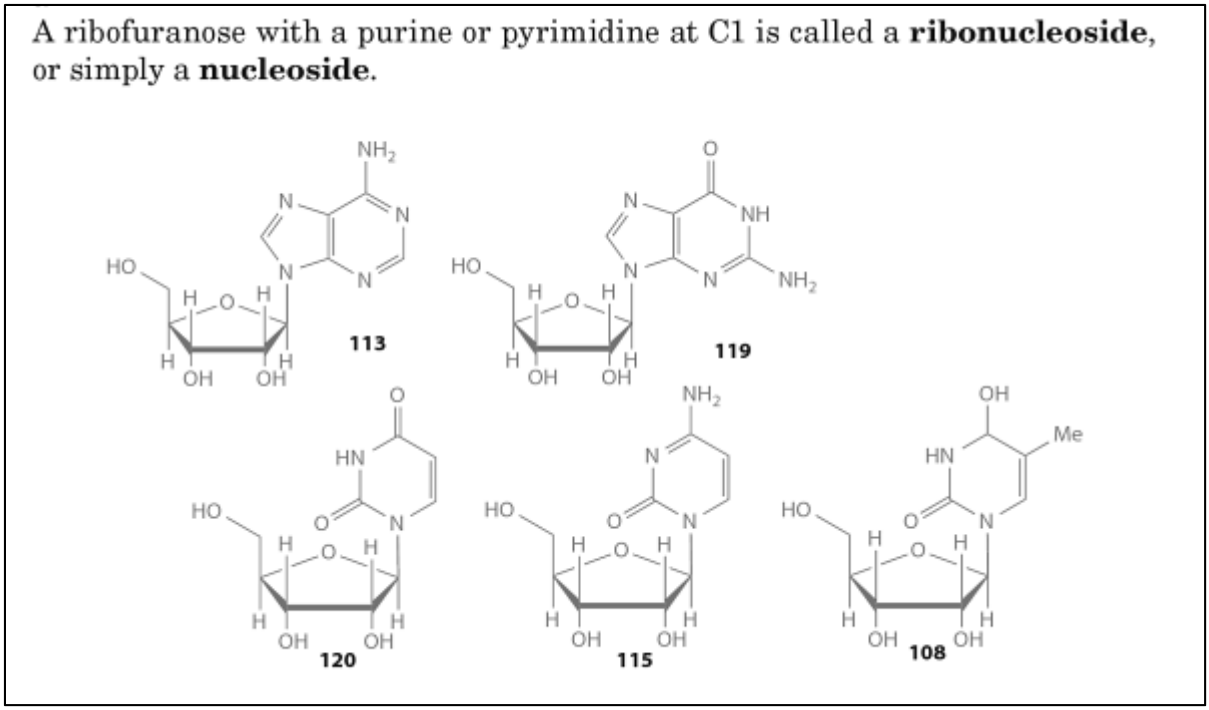


Figure 23. Definition of ribonucleoside from *Organic Chemistry*.

87. This text describes a ribonucleoside as a ribose sugar coupled to a base. The illustration demonstrates the presence of hydroxyl groups (OH) at both the 2′ and 3′ positions, as required by the term "ribofuranose."

88. As another example, *Stedman's Medical Dictionary* also provides a definition for ribonucleoside: "[a] nucleoside in which the sugar component is ribose." STEDMAN'S MEDICAL DICTIONARY 1571 (Maureen Barlow Pugh et al. eds., 27th ed. 2000) (Ex. M). The text goes on to define "ribose" as "[t]he pentose that, as in the D-isomer, is present in ribonucleic acid." *Id.* As shown in Figure 7 above, ribose as present in ribonucleic acid contains hydroxyl groups at 2′ and 3′ down positions.

89. Collectively, these references use the term "ribonucleoside" synonymously with a base coupled to ribose. Skilled artisans would have had the same understanding of ribonucleoside. Thus, the term "β-D-2-C-branched pyrimidine ribonucleoside" refers to a ribose

nucleoside coupled to pyrimidine in a β-D configuration that is also "2 ′-C-branched."

B. Definition of "2′-C-branched pyrimidine ribonucleoside"

90. Also as described above, skilled artisans would have understood the term "2′-C-branched" in the context of "β-D-2′-C-branched pyrimidine ribonucleoside" in claim 26 of the '054 to exclude fluorine from the 2′ down position. First, as explained above, the use of the term "ribofuranose" requires a hydroxyl group – not a fluorine – oriented down at the 2′ position. Second, skilled artisans reading the specification would have understood that fluorine is excluded from the 2′ down position. See paragraphs 78-81. Despite the use of the term "fluoro" hundreds of times in the specification, including at the 2′ up position, not once is "fluoro" identified as a possible substituent at the 2′ down position. Collectively, the term "β-D-2′-C-branched pyrimidine ribonucleoside" in the context of the '054 patent specification excludes fluorine at the 2′ position.

91. Other portions of the specification of the '054 patent further inform my understanding of the definition of "β-D-2′-C-branched pyrimidine ribonucleoside." The patent states:

> In a particular embodiment, the **2′-C-branched ribonucleoside** is desired. The synthesis of a ribonucleoside is shown in Scheme 3. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed **ribonucleoside** can optionally be protected by methods well known to those skilled in the art, as taught by Green et al. *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition, 1991, and then the **2′-OH** can be reduced with a suitable reducing agent.

('054 Patent 48:24-34 (emphasis added).) Thus, Scheme 3, depicted below (red circles added), illustrates the synthesis of a 2′-C-branched ribonucleoside, in which the 3′ and 5′ hydroxyl groups are optionally masked with protecting groups and the 2′ hydroxyl group is removed to produce a deoxyribonucleoside:

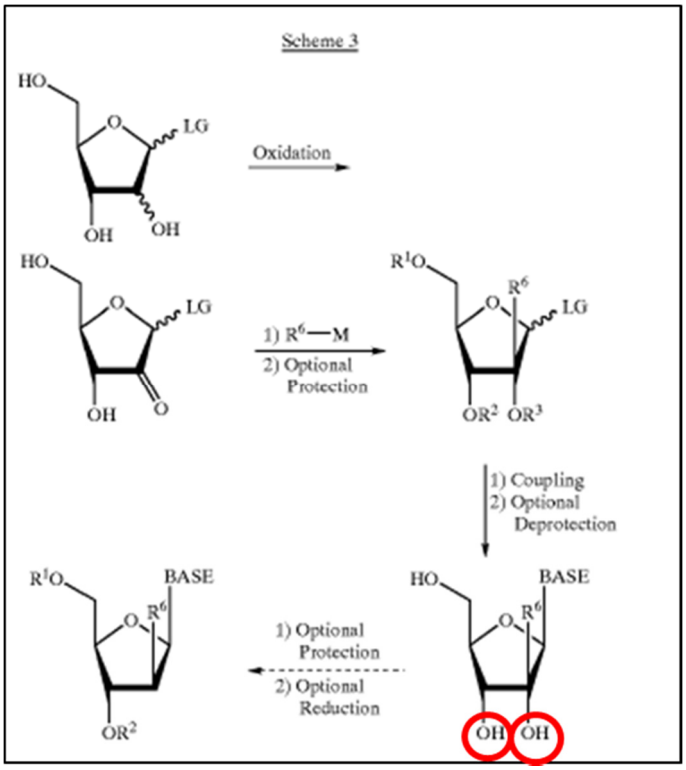


Figure 24. Scheme 3 from the '054 patent showing the synthesis of a 2′-C-branched ribonucleoside.

92. Notably the 2′-C-branched ribonucleoside depicted in Scheme 3 (and highlighted by the red circles) contains hydroxyl groups at the 2′ down and 3′ down positions, not fluorine, consistent with the understanding of the term by those of skill in the art.

93. In my opinion, Idenix's proposed definition of "β-D pyrimidine ribonucleoside having a non-hydrogen substituent at the 3′ down position and two **non-hydrogen** substituents at the 2′ position, at least one of which is connected at the 2' position through a carbon-to-carbon bond" fails to acknowledge that a ribonucleoside has a ribose sugar and therefore has hydroxyl groups at the 2′ and 3′ down positions. I also disagree with Idenix's definition because it omits the requirement that the 2′ down position not contain a fluoro group. The 2′ down position cannot contain a fluoro group because the 2′ down position must contain a hydroxyl and because, in any event, the specification excludes fluoro from that position.

VIII. THE TERM "ADMINISTERING" AS USED IN THE CLAIMS OF THE '054, '597 AND '600 PATENTS

A. "Administering" has a plain and ordinary meaning

94. The term "administering" has a plain and ordinary meaning in the art: providing externally, for example, orally. This term is not used to refer to those compounds, such as metabolites, formed by *in vivo* transformation.

95. The term "administering" is conventionally understood to relate to providing compounds externally to patients or animals. It is not understood to include any subsequent *in vivo* transformations of those compounds. For example, as discussed above in Section III, certain compounds, such as prodrugs, are designed to undergo transformations to form other compounds via enzymatic or non-enzymatic pathways after administration to a patient. Thus, a chemist may synthesize a prodrug compound with the intention that it transform into other compounds after "administering" the prodrug, or providing the prodrug externally, to the patient.

96. This plain and ordinary meaning of "administering" to one of skill in the art is consistent with general purpose dictionary definitions. For example, the American Heritage Dictionary defines "administer" as "[t]o apply as a remedy" and "[t]o mete out; dispense," words associated with externally provided compounds, not metabolites formed *in vivo*. THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE 22 (Houghton Mifflin Co. 4th ed. 2000) (Ex. N).

B. The intrinsic evidence aligns with the plain and ordinary meaning of "administering"

97. My review of the intrinsic evidence, especially the patent specifications of the '054, '597, and '600 patents, further supports my opinion that the term "administering" does not encompass metabolites formed *in vivo*. For example, the specifications use the term to refer to externally providing a prodrug compound that ultimately releases a parent compound *in vivo*. See

paragraph 44. The specifications state that "[t]he active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself." ('054 Patent 36:53-56; '600 Patent 110:2-5; *see also* '054 Patent 38:58-63; '600 Patent 109:44-49).

98. The specifications also discuss dosage forms of administered compounds, which are inapposite for metabolites formed *in vivo* and further confirm my opinion regarding the plain and ordinary usage of "administering" in these patents. For instance, the specifications state that dosage units "can be ***administered*** by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form." ('054 Patent 41:62-65; '600 Patent 116:45-47 (emphasis added).) Specifically, "[f]or the purpose of oral therapeutic ***administration***, the active compound[s] can be incorporated with excipients and used in the form of tablets, troches, or capsules." ('054 Patent 42:39-42; '600 Patent 117:31-34 (emphasis added).)

99. In my view, Idenix's proposed definition for "administering" of "making available" is overly broad to the extent that it includes metabolites formed *in vivo*. A metabolite of an administered compound that is created by *in vivo* transformation is not "administered." Idenix's construction is inconsistent with the way the term was used in the art and unsupported by the patents' specifications.

IX. CONCLUSION

100. This Declaration is based on my study of the information available to me at the time of its writing. My review and consideration of the Idenix patents, their claims, and the other materials discussed in this Declaration, including the relevant literature, are ongoing. As my analysis continues, I may identify additional evidence supporting the opinions that I have summarized in this Declaration. I reserve the opportunity to update, supplement, or amend this

Declaration in view of further analysis or additional information that might be obtained or become available at a later time or to address new or different positions taken by Idenix.

Dated: June 23, 2015

Jason Micklefield, Ph.D.